

screening the collection of mutant proteins to identify at least one mutant protein whose ability to activate T cells is reduced compared with that of the viral protein; and

screening the collection of mutant proteins to identify those that successfully participate in a biological activity selected from the group consisting of viral infection, viral capsid assembly, and cell entry by virus expressing mutant protein,

so that mutant proteins that have reduced T cell stimulatory activity yet retain activity within the virus are identified.

105. The method of claim 104, wherein the step of providing comprises:

providing the gene encoding the viral protein; and

exposing the gene to mutagenesis conditions so that mutations are introduced randomly within the gene sequence and the collection of mutant genes is produced, which collection is characterized by a random distribution of sequence alterations as compared with the gene encoding the viral protein.

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### Remarks

The present application is a Continued Prosecution Application of a parent case in which all of the pending claims stood rejected for lack of written description, indefiniteness, lack of novelty and/or obviousness. All of the previously-pending claims have been cancelled, rendering the rejections levied against them moot. Nonetheless, Applicant addresses the rejections in order to demonstrate their inapplicability to the present, newly-added claims. Each of the rejections is addressed individually below.

### Lack of Written Description under 35 USC § 112, ¶ 1

Several claims in the parent case were rejected for lack of written description of the phrases (i) ". . . first polypeptide, while retaining at least one desirable characteristic of the first polypeptide"; and (ii) "wherein either or both the antibody reactivity and the alteration in the antibody reactivity are associated with an undesirable immune response".

The cited language is not present in the currently-pending claims. However, the claims do encompass methods in which (i) a mutant polypeptide retains at least one desired biological activity; and/or (ii) antibody reactivity (e.g., IgE binding or IgG binding) is associated with an undesirable immune response (e.g., allergy or reduction in therapeutic activity) is associated with an undesirable immune response. Applicant respectfully submits that these ideas, and this language, can be found at many points within the specification.

For example, the first sentence of the Summary of the Invention states "disclosed is a method for reducing or preventing undesirable immune responses by generating and/or identifying mutant polypeptides that fail to elicit, or elicit less of, an undesirable immune response while retaining one or more desired characteristics" (pg. 3, lines 5-8). The Summary of the Invention also provides substantial discussion of types of "undesirable immune responses" (see, for example, page 3, line 25-page 5, line 17). Further amplification is provided in the Description (see, for example, page 10, line 27-page 14, line 7). The application also provides extensive description of how undesirable immune responses may be detected and/or assayed (see, for example, Section C, beginning on page 18, line 7). Additionally, the application provides a detailed discussion of possible retained desired characteristics and their detection and/or assay (see, for example, Section E, beginning on page 24, line 7)

Applicant respectfully submits that the present application contains a complete written description of the presently claimed invention.

**Indefiniteness under 35 USC § 112, ¶ 2**

Various claims in the parent application were rejected for indefiniteness under 35 USC § 112, ¶ 2. The cited indefinite language is not present in the newly-added claims, so that this rejection is inapplicable to the pending claims.

**Lack of Novelty over Hakkart et al.**

Certain of the claims in the parent application were rejected for lack of novelty over Hakkart et al. As discussed previously, Hakkart et al. describes the generation of Der p 2 mutants by site-directed mutagenesis of predicted antigenic sites. IgE binding to these mutants was then studied. This reference cannot anticipate the present claims.

With regard to claim 89, Hakkart et al. do not teach or suggest any "screening . . . to identify those [mutant allergen proteins] that retain at least one desired biological activity". Furthermore, with regard to claim 93, Hakkart et al. does not teach or suggest "exposing the gene to mutagenesis conditions so that mutations are introduced *randomly* . . . ". By contrast, Hakkart et al. discuss only site directed mutagenesis. Also, Hakkart et al., provide no teaching or suggestion of a method relating to therapeutic proteins whose therapeutic activity is reduced by IgG binding (claim 98), or of a method relating to viral proteins (claim 104).

**Lack of Novelty over Smith et al.**

Certain of the claims of the parent application were rejected for lack of novelty over Smith et al. Smith et al. describes the purification of a Der p 2 mutant that contains an arginine

substitution at position 73. This mutant was tested for its ability to cause a wheal on intradermal skin testing and for its ability to stimulate T cell proliferation. This reference cannot anticipate the present claims.

With respect to claim 89, Smith et al. does not describe "providing a collection of mutant genes . . . ". Rather, Smith et al. begins with a single, purified mutant protein. Smith et al. therefore does not teach or suggest any of the steps relating to screening "a collection". Also, like Hakkart et al., Smith et al. provides no teaching or suggestion of of a method relating to therapeutic proteins whose therapeutic activity is reduced by IgG binding (claim 98), or of a method relating to viral proteins (claim 104).

#### **Lack of Novelty over Jespers et al.**

Certain of the claims of the parent application were rejected over Jespers et al. Jespers et al describes random mutagenesis of a staphylokinase gene by error-prone PCR, and the production of mutant proteins in a phage display library. The library was then tested for binding to two different murine monoclonal antibodies in order to determine whether the epitopes recognized by the antibodies were disrupted by the mutagenesis. The library was also tested for binding to plasmin in order to remove globally misfolded members. This reference cannot anticipate the present claims.

First, Jespers et al. provide no teaching or suggestion that is relevant to allergen proteins (claim 89) or viral proteins (claim 104). Of course, Jespers et al. does discuss streptokinase, which is a therapeutic protein. However, Jespers et al. does not teach "screening the collection of mutant proteins to identify at least one mutant protein whose affinity for anti-therapeutic-polypeptide IgG is reduced . . . ". Since Jespers et al. is concerned with mapping conformational

epitopes, the authors utilize readily-available murine monoclonal antibodies that are not shown to be related to any IgG that might interfere with streptokinase's therapeutic potential.

**Obviousness over Hakkart et al. in view of Steinberger et al**

Certain of the claims in the parent application were rejected over Hakkart et al in combination with Steinberger et al. As discussed above, Hakkart et al. does not teach or suggest screening to identify mutant proteins that retain a desired biological activity. Nor does it teach exposing an allergen protein gene to mutagenesis conditions. Furthermore, Hakkart et al. provides no teachings relevant to therapeutically active proteins or viral proteins.

Steinberger et al. cannot remedy these deficiencies of Hakkart et al.; the combination of Hakkart et al. with Steinberger et al. therefore cannot render obvious the present invention. Steinberger et al. describes the preparation of a combinatorial library of IgE molecules from an allergic patient. Steinberger et al. provides no teaching or suggestion of mutant allergen genes or proteins at all, let alone of methods including a step of screening to identify mutant allergen proteins that retain a desired biological activity, or of methods including a step of exposing an allergen protein gene to mutagenesis conditions.

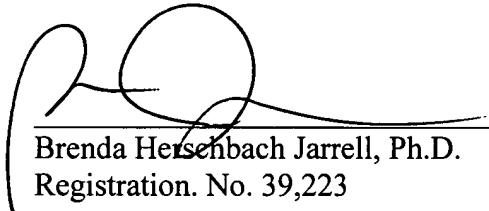
**Obviousness over Hakkart et al. in view of Espanion et al**

Certain of the claims in the parent application were rejected for obviousness over Hakkart et al in view of Espanion et al., which is cited as teaching the production of proteins in transgenic animals. Whether or not Espanion et al. teaches such production, that teaching could not render the above-identified defects in Hakkart et al., so the combination of Hakkart et al. with Espanion et al. cannot render obvious the presently claimed invention.

In light of the present Amendment and Remarks, Applicant respectfully submits that the present case is in condition for allowance; a Notice to that effect is requested.

Please charge any fees that may be associated with this matter, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted



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## Appendix

### **CLAIMS AS PENDING AFTER ENTRANCE OF THE PRESENT AMENDMENT**

89. A method comprising steps of:

providing a collection of mutant allergen genes that differ in sequence from a gene encoding a naturally-occurring allergen protein in that each of the mutant allergen genes contains one or more nucleotide deletion, addition, or substitution as compared with the gene encoding the naturally-occurring allergen protein;

expressing a collection of mutant allergen proteins from the collection of mutant allergen genes;

screening the collection of mutant allergen proteins to identify at least one mutant allergen protein whose affinity for anti-allergen IgE is reduced as compared with that of the naturally-occurring allergen protein; and

screening the collection of mutant allergen proteins to identify those that retain at least one desired biological activity,

so that mutant allergen proteins that have reduced IgE binding and yet retain the at least one desired biological activity are identified.

90. The method of claim 89, wherein the at least one desired biological activity is selected from the group consisting of T cell stimulatory activity; IgG binding activity; and ability, when administered to an individual sensitive to the naturally-occurring allergen protein, to promote desensitization of the individual to the naturally-occurring allergen protein.

91. The method of claim 89, wherein the naturally-occurring allergen protein contains at least one conformational epitope.

92. The method of claim 89, wherein the step of providing a collection of mutant allergen genes comprises providing at least one mutant allergen gene that contains a mutation disrupting a conformational epitope.

93. The method of claim 89, wherein the step of providing comprises:  
providing the gene encoding the naturally-occurring allergen protein; and  
exposing the gene to mutagenesis conditions so that mutations are introduced randomly within the gene sequence and the collection of mutant allergen genes is produced, which collection is characterized by a random distribution of sequence alterations as compared with the gene encoding the naturally-occurring allergen protein.

94. The method of claim 89, wherein the step of screening the collection of mutant allergen proteins to identify at least one mutant allergen protein whose affinity for anti-allergen IgE is reduced as compared with that of the naturally-occurring allergen protein comprises:

providing a collection of IgEs or Fabs representing those expressed in an individual who is allergic to the naturally-occurring allergen protein; and  
detecting binding of IgEs or Fabs from the collection to mutant allergen polypeptides as compared with naturally-occurring allergen protein.

95. The method of claim 94, wherein the individual who is allergic to the naturally-occurring allergen protein is a human individual.

96. The method of claim 89, 94, or 95 wherein the naturally-occurring allergen protein comprises a polypeptide that is naturally found in a source selected from the group consisting of insects, foods, molds, dusts, pollens, plants, fish, shellfish, and mammals.

97. The method of claim 95, wherein the naturally-occurring allergen protein comprises a polypeptide that is naturally found in a food.

98. A method comprising steps of:

providing a collection of mutant genes that differ in sequence from a gene encoding a therapeutic polypeptide whose therapeutic activity is reduced by IgG binding in that each of the mutant genes contains one or more nucleotide deletion, addition, or substitution as compared with the gene encoding the therapeutic polypeptide;

expressing a collection of mutant proteins from the collection of mutant genes;

screening the collection of mutant proteins to identify at least one mutant protein whose affinity for anti-therapeutic-polypeptide IgG is reduced as compared with that of the original therapeutic polypeptide; and

screening the collection of mutant proteins to identify those that retain therapeutic activity,

so that mutant proteins that have reduced IgG binding and yet retain therapeutic activity are identified.

99. The method of claim 98, wherein the step of providing comprises:

providing the gene encoding the therapeutic polypeptide; and

exposing the gene to mutagenesis conditions so that mutations are introduced randomly within the gene sequence and the collection of mutant genes is produced, which collection is characterized by a random distribution of sequence alterations as compared with the gene encoding the therapeutic polypeptide.

100. The method of claim 98, wherein the step of screening the collection of mutant proteins to identify at least one mutant protein whose affinity for anti-therapeutic-polypeptide IgG is reduced comprises:

providing a collection of IgGs or Fabs representing those expressed in an individual in whom the therapeutic activity of the therapeutic protein is reduced by IgG binding; and

detecting binding of IgGs or Fabs from the collection to mutant proteins as compared with the therapeutically active protein.

101. The method of claim 95, wherein the therapeutic polypeptide is selected from the group consisting of GM-CSF and streptokinase.

102. The method of claim 100, wherein the therapeutic polypeptide is streptokinase and the therapeutic activity comprises an ability to disrupt blot clots.

103. The method of claim 100, wherein the therapeutic polypeptide is GM-CSF, and the therapeutic activity comprises trophic activity.

104. A method comprising steps of:

providing a collection of mutant genes that differ in sequence from a gene encoding a protein expressed by a therapeutic virus whose therapeutic activity is reduced by clearing, the

mutant genes differing from the viral gene in that each mutant gene contains one or more nucleotide deletion, addition, or substitution as compared with the viral gene;

expressing a collection of mutant proteins from the collection of mutant genes;

screening the collection of mutant proteins to identify at least one mutant protein whose ability to activate T cells is reduced compared with that of the viral protein; and

screening the collection of mutant proteins to identify those that successfully participate in a biological activity selected from the group consisting of viral infection, viral capsid assembly, and cell entry by virus expressing mutant protein,

so that mutant proteins that have reduced T cell stimulatory activity yet retain activity within the virus are identified.

105. The method of claim 104, wherein the step of providing comprises:

providing the gene encoding the viral protein; and

exposing the gene to mutagenesis conditions so that mutations are introduced randomly within the gene sequence and the collection of mutant genes is produced, which collection is characterized by a random distribution of sequence alterations as compared with the gene encoding the viral protein.